Applicant: Virginia W. Cornish Serial No.: 10/705,644 Filed: November 10, 2003

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In the Drawings

Please replace Figs. 15-17 with replacement Figs. 15-17 attached hereto as Exhibit A.

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REMARKS

Claims 133, 135-137, 141-147 and 150-160 are pending, with claims 133, 135-137, 141-147 and 150-157 withdrawn from consideration. By this Amendment, applicant has canceled claims 133, 135-137, 141-147 and 150-157 without prejudice or disclaimer to applicant's right to pursue the subject matter of these claims in the future. In addition, applicant has amended claims 158 and 160, and added new claims 161-180.

Support for the amendments to claim 158 may be found in the specification as filed at, inter alia, page 24, line 32 to page 25, line 21; page 7, lines 2-3; and page 23, lines 27 to 34. Claim 159 has been amended to correct typographical errors. Support for new claim 160 may be found in original claim 140. Support for new claims 161 and 165 may be found in original claim 141; and page 33, line 4 and lines 23-25. Support for new claims 162 and 166 may be found in original claim 142; and page 33, line 4 and lines 23-25. Support for new claims 163 and 167 may be found in original claim 143; and page 33, line 5 and lines 22-25. Support for new claims 164 and 168 may be found in original claim 144; and page 33, line 5 and lines 22-25. Support for new claim 169 may be found in original claim 146; at page 33, lines 29 to 31; and at page 40, lines 25-29. Support for new claim 170 may be found at page 49, lines 20-22; at page 33, lines 30-32; and at page 49, lines 18-20. Support for new claim 171 may be found, inter alia, at page 24, line 32 to page 25, line 21; page 23, lines 27 to 34. Support for new claim 172 may be found in the specification as originally filed at, inter alia, page 24, line 32 to page 25, line 21; page 7, lines 2-3; page 23, lines 27 to 34; original claim 142; and page 33, line 4 and lines 23-25; original claims 143, 144 and 146; page 33, line 5 and

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lines 22-25; at page 33, lines 29 to 31; and at page 40, lines 25-29; page 49, lines 20-22; at page 33, lines 30-32; and at page 49, lines 18-20 . Support for new claim 173 may be found in the specification as originally filed at, inter alia, page 24, line 32 to page 25, line 21; page 7, lines 2-3; and page 23, lines 27 to 34; at page 4, line 35 to page 5, line 25; page 19, lines 18-24; and page 20, lines 20-30. Support for new claim 173 may also be found in the specification of the priority document as originally filed at, inter alia, page 4, lines 29-31; page 4, line 35 to page 5, line 9; page 5, lines 16 to 18; and page 5, lines 11-15. Support for new claim 174 may be found in the specification as originally filed at, inter alia, page 5, lines 10-11; page 29, lines 28-31. Support for new claim 174 may also be found in the specification of the priority document as originally filed at, inter alia, page 5, lines 5-7 and page 20, lines 20-24. Support for new claim 175 may be found in the specification as originally filed at, inter alia, page 9, lines 10-12; Fig. 13; page 33, lines 17 to Support for new claim 175 may also be found in the specification of the priority document as originally filed at, inter alia, page 7, lines 8-13, and Fig. 2. Support for new claim 176 may be found in the specification as originally filed at, inter alia, Fig. 2. Support for new claim 176 may also be found in the specification of the priority document as originally filed at, inter alia, page 7, lines 8-13 and Fig. 2; page 14, line 5-6. Support for new claim 177 may be found in the specification as originally filed at, inter alia, page 24, line 32 to page 25, line 21; page 7, lines 2-3; and page 23, lines 27 to 34; page 4, line 35 to page 5, line 25. new claim 177 for may also be found the specification of the priority document as originally filed at, inter alia, page 4, lines 29-31; page 4, line 35 to page 5,

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line 9; page 5, lines 16 to 18; and page 5, lines 11-15. Support for new claim 178 may be found in the specification as originally filed at, inter alia, page 9, lines 10-11; page 23, lines 13-14; and Fig. 2. Support for new claim 178 may also be found in the specification of the priority document originally filed at, inter alia, page 5, lines 5-7. Support for new claim 179 may be found in the specification as originally filed at, inter alia, page 33, lines 17 to 23. Support for new claim 179 may also be found in specification of the priority document as originally filed at, inter alia, page 7, lines 8-13; and Fig. 2. Support for new claim 180 may be found in the specification as originally filed at, inter alia, Fig. 2. Support for new claim 180 may also be found in the specification of the priority document as originally filed at, inter alia, page 7, lines 8-13; Fig. 2; and page 14, line 5-6.

In addition applicant has herein amended the title, amended the Abstract, and has replaced original Figs. replacement Figs. 15-17. Applicant maintains that this Amendment raises no issue of new Accordingly, matter. applicant respectfully requests entry of this Amendment.

Abstract

In the September 7, 2006 Office Action the Examiner objected to the content of the Abstract. In response, applicant has hereinabove amended the Abstract. Applicant maintains that the amended Abstract complies with 37 C.F.R. §1.72(b).

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Specification

The Examiner objected to specification as requiring an update priority paragraph.

In response, applicant has hereinabove updated the priority paragraph.

The Examiner objected to page 7 of the specification as having only 3 lines of text.

In response, applicant respectfully traverses the Examiner's objection. Applicant notes that there is no preclusion against such an arrangement of text. In addition, it is noted that page 7 of the specification marks the end of the "Summary of Invention" section and it is convention to start a new section on a new page. Accordingly, applicant respectfully requests that the Examiner reconsider and withdraw this objection.

The Examiner objected to the specification as reciting the terms "genomicDNA" and "syntheticDNA".

In response, applicant has hereinabove amended the specification to correct these typographical errors.

The Examiner objected to the title of the invention as non-descriptive.

In response, applicant has hereinabove amended the title to adopt the title suggested by the Examiner in the September 7, 2006 Office Action.

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Sequence Listing

The Examiner stated that the application does not comply with the 37 C.F.R. §§1.821-1.825 in that it allegedly discloses sequence that have not been identified by a sequence identifier. The Examiner asserted that a sequence is disclosed at page 23, line 11.

In response, applicant respectfully traverses the Examiner's rejection. Applicant has reviewed the specification maintains that there are no sequences disclosed the specification that require a Sequencing Listing. In addition there are no sequences at page 23, line 11. Applicant notes that the amino acid sequence disclosed on page 34, line 33 and at page 35, line 14 and line 20 has three (3) amino acids only, and the nucleotide sequence disclosed on page 35, line 22, has six (6) nucleotides only. As such, both of these sequences are excluded from the Sequence Listing requirement under 37 C.F.R. §1.821(a) which require at least four amino acids or ten or more nucleotides. Accordingly, applicant respectfully requests that the Examiner reconsider and withdraw this ground of rejection.

Drawings

The Examiner objected to Figs. 15-17 as too dark to be discernable.

In response, applicant attaches hereto as **Exhibit A** replacement Figs. 15-17 in compliance with 37 C.F.R. §1.121(d).

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Claim Objection

The Examiner objected to claim 159 as reciting the terms "genomicDNA" and "syntheticDNA".

In response, applicant has amended claim 159 to correct these typographical errors.

Claims Rejected Under 35 U.S.C. §112, First Paragraph (Written Description)

The Examiner rejected claims 158-160 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art at the time the application was filed that the applicant had possession of the claimed invention.

In response, applicant respectfully traverses the Examiner's rejection.

Established Nature of Yeast 3-Hybrid System

Applicant initially notes that the current invention is an improvement on the established and widely used 3-hybrid screening assay. Applicant has improved the 3-hybrid screening assay by using a methotrexate moiety as one of the ligands in the chemical inducer of dimerization ("CID") component (also referred to as "hybrid ligand") of the 3-hybrid screening assay.

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As M.P.E.P. §2164.01 states, "a patent need not teach, and preferably omits, what is well known in the art." (emphasis added), citing In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); and Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. 1986), cert. denied, 480 U.S. 947 M.P.E.P (1987). §2163(II)(a)(3) confirms that "what is conventional or well known to one of ordinary skill in the art need not disclosed in detail" (emphasis added), again referring to Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d at 1384, 231 USPQ at 94.

As such. applicant notes that the 3-hybrid system established before the earliest effective filing date of the current application. For example, see Licitra, E.J., and Liu, J.O. (1996), A three-hybrid system for detecting small ligandprotein receptor interactions. Proc. Natl. Acad. Sci. USA 93, 12817-12821 (submitted with the Information Disclosure Statement filed November 10, 2003 in connection with the above-identified application). The Abstract of Licitra et al., and Fig. 2 on page 12819, clearly set forth a 3 hybrid screening system employing two fusion proteins, one comprising a DNA-binding domain and a ligand binding receptor for binding one portion of the hybrid ligand, the other comprising a transactivation domain and a domain that binds the second portion of the hybrid ligand, and a reporter gene system. Applicant further provides hereto as Exhibits 4-7, (which are items also listed in the Supplemental Information Disclosure Statement in this document), a selection of papers published before the earliest effective filing date of the subject application, all employing 3-hybrid systems.

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papers clearly evidence the established nature of system improved by applicant's invention.

In addition, applicant notes that there are already issued patents in this field, for example U.S. Patent Nos. 5,928,868 (submitted with the Information Disclosure Statement filed 2003 in connection with the above-identified November 10, application) and 7,083,918. The '868 patent, which was issued on July 27, 1999, i.e. before the priority date of the current application and which is incorporated by reference into the current application, describes the yeast 3-hybrid system and is based the even earlier established 2-hybrid system. patent describes fusion proteins, DNA-binding domains. genes, and transcriptional activators (e.g. Background regarding the 2-hybrid system components; see Fig. 1, and Examples 2-6 regarding the 3-hybrid system).

Applicant maintains that the Examiner's assertions with regard to the current invention, especially in view of what those of skill in the art readily know and use, fail to take into account the established nature of the field.

Specific Points Raised by the Examiner

In order to expedite prosecution, and without conceding the correctness of the Examiner's position, applicant has herein amended the claims to recite subject matter applicant believes the Examiner will find clearly patentable. Applicant notes initially that the specification provides both the structure of methotrexate (e.g. see Fig. 5) as well as linkers

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comprising methotrexate (e.g. see Fig. 6). 1 Thus, one skilled in the art was aware at the time the application was filed that methotrexate had been extensively studied, and even that a large disclosure of methotrexate analogs that bind to DHFR readily available. was Moreover, it was known that methotrexate can be modified via its g-carboxylate without disrupting its interaction with DHFR (see specification, page 30, lines 5-7). Accordingly, it was clear that methotrexate could be attached at various points, i.e. not only those illustrated in the subject application, yet retain necessary qualities.

Applicant further notes that the level of skill in the art is high, and that "generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement." See M.P.E.P. §2163 (II) (A) (2).

Accordingly, applicant maintains that the claims as amended contain subject matter such that the description in the specification would reasonably convey to one of ordinary skill in the art that the applicant had possession of the claimed invention at the time of filing.

The Examiner also rejected claims 158-160 under 35 U.S.C. §112, first paragraph, on the assertion that the two fusion proteins and DNA reporter gene recited in the claims are allegedly not described in the specification in such a way as

¹ Applicant maintains that subject matter not claimed upon entry of this Amendment is also patentable. However, for expeditious prosecution, applicant intends to pursue such subject matter in a continuation and respectfully looks forward to the allowance of the subject matter claimed herein.

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to reasonably convey to one skilled in the relevant art at the time the application was filed that the applicant had possession of the claimed invention.

In order to expedite prosecution, and without conceding the correctness of the Examiner's position, applicant has herein clarified the claims to recite the characteristics of the first and second fusion proteins. Applicant notes that the first fusion protein comprises (i) a dihydrofolate reductase which is capable of binding methotrexate and (ii) either a transcription activator domain or a DNA binding domain.

First, as noted above, 3-hybrid systems are established and widely used and well-described, and therefore do not need to be described in detail (M.P.E.P §2163(II)(a)(3)). Examples of each of these domains are recited in the specification and are also well-known to those of ordinary skill in the art. Nonetheless, applicant has described dihydrofolate reductase as a binding domain for methotrexate which is fully described in the specification. For example, see page 29, line 28 to page 30, line 7; and Fig. 13. Furthermore, the first fusion protein also comprises a transcription activator domain or a DNA binding domain. Applicant maintains that it is not a tenable position that those of ordinary skill in the art would recognize that such domains are described in specification, especially in light of the exemplified embodiments as well as the common knowledge in the art. Applicant refers the Examiner to the established state of the field as described hereinabove. Applicant also notes that relevant description may be found, inter alia, in Figs. 2, 13 lines 1-23; page and 14; page 18, 33, lines 17 to 32. Applicant further notes that the second fusion protein further

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comprises the protein being identified as binding to the ligand, and so is necessarily understood by those of skill in the art to be the protein of interest.

With regard to the DNA reporter gene, the specification at page 39, line 17 to page 40, line 24, clearly describes such reporter gene systems and notes commercial availability of reporter genes. specification further discusses that The "reporter gene" is a term commonly used in the art familiar to those skilled in the art, e.g. see U.S. Patent Nos. 5,928,868 and 7,083,918. In view of this, applicant again notes that, as M.P.E.P. §2164.01 states, "a patent need not teach, and preferably omits, what is well known in the art." (emphasis added), citing In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); and Hybritech, Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, (Fed. Cir. 1986), cert. denied, 480 U.S. M.P.E.P 2163(II)(a)(3) confirms that "what is conventional or well known to one of ordinary skill in the art need not be disclosed in detail" (emphasis added), again referring to Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d at 1384, 231 USPQ at 94. Applicant maintains, with regard to the Examiner's citation of University of California v. Eli Lilly and Co., 43 USPQ2d1398, 1406 (1997), that reporter recited in the method claimed by applicant are of sequence. For example, the LacZ or Ura3 reporter genes. Unlike the structure of the scope of the cDNAs in the cited case, the structure (sequence) of, for example, commercially available, reporter genes and others is already known, the descriptor "reporter" merely informs one of skill in the art as to the class of genes to employ, genes which have already been established.

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Moreover, applicant notes that M.P.E.P. §2163(II)(A)(3)(A) notes that "As explained by the Federal Circuit [...] 'there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure.' Falkner v. Inglis, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006). See also Capon v. Eshhar, 418 F.3d at 1358, 76 USPQ2d at 1084 ('The Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes' where the genes were novel combinations of known DNA segments.)" (Emphasis added).

Applicant maintains that the claimed subject matter is clearly described in the specification in such a way as to reasonably convey to one skilled in the relevant art at the time the application was filed that the applicant had possession of the claimed invention. Accordingly, applicant respectfully requests that the Examiner reconsider and withdraw this ground of rejection.

Claims Rejected Under 35 U.S.C. §112, First Paragraph (Enablement)

The Examiner rejected claims 158-160 under 35 U.S.C. §112, first paragraph, as allegedly not enabled by the specification. The Examiner asserted that the specification, while being enabling for the Dex-Mtx dimerization system used to induce LexA-GR and DHFR-B42 and the use of a lacZ reporter, does not reasonably provide enablement for the use of any

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screening molecule with any set of fusion proteins or any analogs of methotrexate.

In response, applicant respectfully traverses the Examiner's Initially, rejection. applicant notes that the invention is an improvement on established 3-hybrid systems, with the identification of the advantages of a CID comprising a methotrexate or methotrexate analog. As 3-hybrid systems are established and widely used and well-described, they therefore need to be described in detail §2163(II)(a)(3)). In fact, such description is preferably omitted (M.P.E.P. §2164.01). As such, and as noted above, applicant notes that there is already a literature in the art (see Licitra et al. and Exhibits B-E for example) as well as the issued patents in this field, for example U.S. Patent Nos. 5,928,868 (submitted with the Information Disclosure Statement filed November 10, 2003 in connection with the aboveidentified application) and 7,083,918. The '868 patent was issued on July 27, 1999, before the priority date of current application, and is directed to a three-hybrid screening assay. Applicant further notes that that U.S. Patent Nos. 5,928,868 is incorporated by reference into the current application. Applicant maintains that the Examiner's assertions with regard to the current invention fail to take into account the established nature of the field.

Specifically, the Examiner stated that the amount of experimentation required to practice the claimed invention is undue as the claims encompass an unspecified amount of methotrexate analogs.

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In order to expedite prosecution, and without conceding the correctness of the Examiner's position, applicant has herein amended the claim to remove the phrase "methotrexate analog"

The Examiner also asserted that the claimed method is directed to covalent binding of a ligand with specificity to the unknown protein target which renders the claimed method as inoperable because specificity would require that the target protein is known.

Applicant has herein amended the claims to clarify the claimed subject matter, and have deleted the term "unknown protein target".

The Examiner also stated that the claimed method utilizes at least two fusion proteins and a DNA with a reporter gene which are only described functional terms as no correlation is allegedly made between structure and function.

Applicant has herein amended the claims to recite the first fusion protein comprises a dihydrofolate reductase. Such binding domains are finite and are known in the art. The claims as amended also recite a second fusion protein comprising the protein being tested, which is necessarily known of course. Applicant further notes that various examples of the fusion proteins are set forth in the specification at, inter alia, page 18, lines 1 to 23.

Furthermore, one of the first and second fusion proteins also comprises a transcription activator domain and the other comprises a DNA binding domain. Such domains are well known in

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the art and are exemplified in the specification, as are reporter genes.

Applicant notes that each of the transcription activator domain, the DNA binding domain, and the reporter genes are established technologies. Applicant notes that reporter genes and transcription activator domain were already established with the yeast two-hybrid system which preceded the yeast 3 hybrid system - e.g. see "Background of Invention" in U.S. Patent No. 5,928,868, and further note that such terms are standard in the art (e.g. see claims 1, 10 and 15 of U.S. Patent Nos. 5,928,868, see Exhibits B-E). Thus, applicant maintains that it is not tenable that one of skill in the art would somehow not know how to make and use the claimed invention based on the specification.

With regard to the Examiner's assertion that the state of the art is unpredictable, which applicant does not concede, it is M.P.E.P. noted that §2164.01 states "the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation". Moreover, the experimental techniques employed in Adiba et al. those employed and set forth in the application. Applicant maintains that no undue experimentation is required.

Given this, and the examples set forth in the specification, including the working example, and the skill in the art, no undue experimentation would be required by the skill artisan for enablement of the claimed method.

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Claims Rejected Under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 158-160 under 35 U.S.C. §112, second paragraph, as failing to set forth the subject matter which applicant regards as her invention.

The Examiner asserted that claim 158 is incomplete. The Examiner stated that the claimed method does not include a step to isolate or recover said protein target. The method is for identifying a target protein as being able to bind a ligand.

In response, applicant respectfully traverses the Examiner's rejection. However, in order to expedite prosecution, and without conceding the correctness of the Examiner's position, applicant has herein amended the claims to clarify the claimed subject matter. Applicant notes that as amended, the method recited in claim 158 does not require a step of recovering the protein.

The Examiner asserted that it is unclear whether the "methotrexate moiety" is also covalently bonded to a ligand or just the "analog of methotrexate" is.

In response, applicant respectfully traverses the Examiner's rejection. However, in order to expedite prosecution, and without conceding the correctness of the Examiner's position, applicant has herein removed reference to an "analog of methotrexate" in the claim. In addition, the claim as amended clarifies that the methotrexate is covalently bound to the ligand.

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The Examiner further stated that item (d) is confusing for the recitation of "selecting which cell expresses the reporter gene" in view of item (b).

In response, applicant respectfully traverses the Examiner's rejection. However, in order to expedite prosecution, and without conceding the correctness of the Examiner's position, applicant has herein amended claim 158 to clarify in step (d) "selecting the cell if it expresses the reporter gene". As amended, applicant maintains that the claim is not indefinite.

The Examiner also stated that claims 158 and 160 are indefinite for the recitation of "a ligand which has a specificity for an unknown protein target" in claim 158.

In response, applicant respectfully traverses the Examiner's rejection. However, in order to expedite prosecution, and without conceding the correctness of the Examiner's position, applicant has herein amended claim 158 to remove the "phrase "specificity for an unknown protein target". As amended, applicant maintains that the claim is not indefinite.

In light of the amendments and arguments made above, applicant respectfully requests that the Examiner reconsider and withdraw this ground of rejection.

Claims Rejected Under 35 U.S.C. §102(b)

The Examiner rejected claims 158-160 under 35 U.S.C. §102(b) as anticipated by Lin et al., J. Am. Chem. Soc. 122:4247-4248 (2000).

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In response, applicant respectfully traverses the Examiner's rejection. Applicant notes that for a reference to be available under 35 U.S.C. §102(b) it must, inter alia, have been available "more than one year prior to the date of application for patent in the United States". Applicant notes that the current application has a priority date of January 2000. As shown above, the current claims are supported by, and thus have the effective filing date of, the January 24, 2000 application. Accordingly, Lin et al. is not available under 35 U.S.C. §102(b). Applicant therefore respectfully requests that the Examiner reconsider and withdraw this ground of rejection.

SUPPLMENTAL INFORMATION DISCLOSURE STATEMENT

In accordance with her duty of disclosure under 37 C.F.R. §1.56, applicant directs the Examiner's attention to the following references listed on the attached Form PTO-1449 (Exhibit B). Reference 1 is a U.S. Patent. No copy of this reference is attached hereto, as permitted under 37 C.F.R. §1.98(a)(2)(ii). Copies of references 2-8 are attached hereto as Exhibits 1-7, respectively.

- U.S. Patent No. 7,083,918, Althoff et al., issued August 1, 2006;
- 2) Simons, S. et al., (1981) Dexamethasone 21-Mesylate: An Affinity Label Of Glucocorticoid Receptors From Rat Hepatoma Tissue Culture Cells, *Biochemistry* 78(6):3541-3545;
- 3) Fan, J. et al. (1989) Covalent Labeling of Dihydrofolate Reductase and Folate Transport Proteins by Fluorescein

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Methotrexate, Chemistry and Biology of Pteridines, 1990 Walter de Gruyter & Co., pages 1162 - 1165;

- 4) Lin et al. (2000) Dexamethasone 21-Mesylate: An Efficient Chemical Inducer of Protein Dimerization In Vivo, J. Am. Chem. Soc. 122: Supplemental Information Pages S1-S12;
- 5) Van Criekinge et al. (1998) Use of the Three-Hybrid System as a Tool to Study Capsases, Anal. Biochem. 263(1);
- Bacharach et al. (1998) Binding of Human Immunodeficiency
 Virus Type 1 Gag Protein to the Viral RNA Encapsidation
 Signal in the Yeast Three-Hybrid System, J. Virol.
 72(8):6944-6949;
- 7) Sengupta et al. (1999) Identification of RNAs that bind to a Specific Protein Using the Yeast Three-Hybrid System, RNA 5:596-601; and
- 8) Vidal et al. (1999) Yeast Forward and Reverse 'n'-Hybrid Systems Nuc. Acid Res. 27(4):919-929.

Applicant requests that the Examiner review the above publication and patent applications and make them of record in the subject application. Applicant is submitting this Information Disclosure Statement under 37 C.F.R. §1.97(c) and a check for ONE HUNDRED EIGTHY DOLLARS (\$180.00) is enclosed.

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No fee, apart from the enclosed fee of \$180.00 for filing an Information Disclosure Statement, is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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